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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

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DETAILED ACTION

With supplemental amendment, filed 6/4/2010, in response the office action, mailed on 3/4/2010, the applicants amended claims 1 and 6. Claim 1-6, 8, 22 and 24-40 are pending . Applicants' after final amendment filed on 6/4/2010 has been entered because it does not raise any new issue, or new matter.

Applicants' arguments filed on 6/4/2010, in response to a previous office action mailed on 3/4/2010,, have been fully considered but they are found unpersuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8, 22 and 24-40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208, from IDS) in view of Moutiez et al (Analyst 1997, 122, pp 1347-1352) and Li et al. (J. Am. Soc. Mass spectro. 1997, 8, pp 781-792) as explained in prior office action and stated again below:

Aebersold et al. teach a method of identification and quantification of a protein in a sample by cleaving the protein to peptides using a proteolytic enzyme (page 18, pargh. 4) and using a reagent A-L-PRG, wherein A is linked to a solid support

(wherein, A comprises biotin, oligohistidine, etc, page 12) and is covalently linked to linker L (L contain metal bound chelate, page 14, 2nd parg. and may contain disulfide group, which is cleavable, page 6, last pargh.); PRG comprises a sulfhydryl group, or an enzyme substrate (page 6, 2nd pargh.) N- hydroxysuccinimide ester groups, etc (claim 32 of Aebersold et al.) to bind to the cleaved peptides. Aebersold et al. teach the use of a tandem technique comprising electrospray ionization mass spectrometry coupled with liquid chromatography (HPLC/ESI-MS/MS (FIG 7), peptide sequence information (page 19, 2nd pargh.) combined with isotope tags for qualitative and quantitative analysis of the protein in a sample. Although Aebersold et al. teach the use of a linker L being labeled with isotopes, they do not label the proteins with said isotope. The A-L-PRG reagent of Aebersold et al (similar to applicants' A-Y-PRG) comprises a chelated metal ion and the stable isotope in their L and use the stable isotope as standard in mass spectrometric analysis. However Aebersold et al. do not use a reagent A-Y-PRG wherein said reagent is not isotopically labeled and hence does not use metal ion as a standard in mass spectrometric analysis.

Use of metal ion as a standard in mass spectrometric studies is well known in the prior art (see page 781, Li et al.). Li et al. teach a well characterized spectra of peptide bound silver ion in mass spectral analysis (Figure 1, page 783.)

It is well known in the art the advantage of purifying and detecting proteins using chelated metal tags comprising various metal ions (Porath et al Prot express and Pur. 1992, 3, 263-281, from IDS) using a variety of chelating agents, such as lanthanide metal ions with DOTA (Moutiez et al). Moutiez et al teach a Gd^{3+} ion chelated to

DOTA and teach its separation using metal ion chelate affinity chromatography (page 1350 2nd column) and teach that lanthanide metal complex can be detected using luminescence technique (page 1347 2nd column 2nd paragraph).

Therefore in order to identify and quantify proteins in proteomic samples, one of ordinary skill in the art is **motivated** to modify the A-L-PRG of Aebersold et al with Gd^{3+} DOTA chelate not being modified by isotope label and use the metal ion as standard (as taught by Li et al) in the method of Aebersold et al, because a peptide sample attached to L-PRG with Gd^{3+} DOTA can be separated by metal ion chelate affinity column by HPLC, and optionally can be detected by luminescence before passing into the mass spectrometer.

As such, it would have been obvious to one of ordinary skill in the art to combine the teachings of Aebersold et al, Moutiez et al and Li et al to make an A-L-PRG regent having Gd^{3+} DOTA complex in L, use it in the method of identification and quantification of proteins in a sample by a tandem technique comprising electrospray ionization mass spectrometry coupled with liquid chromatography (HPLC/ESI-MS/MS (FIG 7), peptide sequence information using Gd metal ion as standard, and optionally detecting the Gd^{3+} DOTA attached polypeptide by using luminescence before passing the sample into the Mass spectrometer.

Arguments and response

Applicants' argue, at pages 8-12 of their amendment of 6/04/010, that their method of identification and quantification of a protein in a sample using a tandem technique comprising electrospray ionization mass spectrometry coupled with liquid

chromatography (HPLC/ESI-MS/MS and peptide sequence information combined with metal tags for qualitative and quantitative analysis of the protein in a sample is not obvious over the cited references. Applicants' arguments filed on 6/04/010 have been fully considered, but they found unpersuasive. Applicants' argue that Aebersold et al used isotope coded affinity tag (ICAT) not a metal-labeled tag and used the chelated metal ion to facilitate ionization in the mass spectrometry. Applicants' argument is considered but found unpersuasive. As admitted by the applicants in their response at page 9 (quoting paragraph 2 on page 14 of Aebersold et al.), Aebersold et al also suggested chelated metal ions. Although Aebersold et al do not use metal ion for identification of labeled peptide, however as explained above other references teach the advantages of using metal ion labeled reagent for identification (Li et al.). As explained above, Li et al. teach a well characterized spectra of peptide bound silver ion in mass spectral analysis. Applicants' argument that Muitiez et al teach away from using the mass spectrometric technique is considered but found unpersuasive. First of all, ICP-MS is a specialized technique used to determine total metal ion, such as total Gd (page 1347) in a sample, not a technique, such as HPLC-MS, to quantify labeled peptide. Therefore the argument is not relevant. Furthermore, Moutiez et al do not teach away from the advantages of mass spectrometric analysis coupled with chromatographic resolution but suggested that a luminescence method comprises the further advantage of having spectroscopic characteristics of the chelated species. It is well known in the art the advantage of purifying and detecting proteins using chelated metal tags comprising various metal ions using a variety of chelating agents, such as

lanthanide metal ions. Therefore in order to identify and quantify proteins in proteomic samples, one of ordinary skill in the art is **motivated** to modify the A-L-PRG of Aebersold et al with Gd^{3+} DOTA chelate not being modified by isotope label and use the metal ion as standard (as taught by Li et al) in the method of Aebersold et al, because a peptide sample attached to L-PRG with Gd^{3+} DOTA can be separated by metal ion chelate affinity column by HPLC, and optionally can be detected by luminescence before passing into the mass spectrometer. Thus, the claimed invention remains *prima facie* obvious over the prior art of record.

Allowable Subject Matter/Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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